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| 09/986,381 | 11/08/2001 | Steven S. Sommer | 1954-360 | 5135 |

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|---|
| HASHEMI, SHAR S |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1637 | |

DATE MAILED: 09/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/986,381 | Applicant(s) SOMMER ET AL. | |
|---|---|---|---|
| | Examiner Shar Hashemi | Art Unit 1637 | |

*-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *20 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☒ Claim(s) *16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Claim Objections*

1. Claim 16 is objected to because of the following informalities: The use of the trademark has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8, 11 & 16-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) The description "exons 5 to 9 of the p53 gene" renders claim 8 indefinite. It is unclear as to whether the description "exons 5 to 9 of the p53 gene" refers to the amplified region in entirety, in part, excluding introns, excluding introns or any possible combination of recited

exons. It is suggested to include a SEQ. ID. Identifier to describe the sequence that is being referred to.

B) The phrase "having an average size of at least about 20 kb" in claim 11 renders claims 11, 17-19 indefinite. It is unclear as to whether the phrase "having an average size of at least about 20 kb" refers to the amplified DNA or the mouse DNA.

C) The term "(Taq/GB-D)" renders claim 16 indefinite. It is unclear as to whether the term "(Taq/GB-D)" is equivalent to Platinum Taq DNA polymerase High Fidelity or another type of DNA polymerase.

***Claim Rejections - 35 USC § 102***

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 & 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Sands et al., "p53 Deficiency Does Not Affect the Accumulation of Point Mutations in a Transgene Target," Proc. Natl. Acad. Sci. USA, 92:8517-8521, August 1995.

Sands et al teach a method for determining mutation load comprise identifying a somatic cell which has accumulated p53 levels, amplifying the DNA of the p53 gene of the selected

somatic cell, and determining the frequency of mutation in amplified DNA (see whole document, especially page 8518-8520). They also teach amplification is conducted in the presence of bovine serum albumin (page 8517).

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 8-11, 15-16 are rejected under 35 U.S.C. 102(e) as being anticipated by Diamandis et al (US 6, 071, 726 June 6, 2000).

Diamandis et al teach a method for determining mutation load comprise identifying a somatic cell which has accumulated p53 levels, amplifying the DNA of p53 gene of the selected somatic cell, and determining the frequency of mutation in amplified DNA (see whole document, especially columns 6-13). They teach in the amplifying step, utilizing two different DNA polymerases. They teach Platinum Taq DNA polymerase and Platinum Taq DNA polymerase (pages col.11 lines 35-65). They teach the sizes of the amplified DNA are at least 1 kb, at least 2

kb, and at least about 20 kb (columns 11-14). They teach the DNA is amplified from exons 5 to 9 of the p53 gene (column 11, lines 1-67).

***Claim Rejections - 35 USC § 103***

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-3, 5, 6, 12-14, 20 & 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Diamandis et al (US 6, 071, 726 June 6, 2000) in view of Taylor et al., "Antigen Retrieval for Immunohistochemistry," Applied Immunohistochemistry, 4(3): 144-166, 1996.

The teachings and suggestions of Diamandis et al have been discussed previously.

Diamandis et al do not teach preparing a paraffin-embedded tissue section and immunohistochemical staining for p53.

Taylor et al teach obtaining a single somatic cell by microdissection from an ethanol fixed, paraffin-embedded tissue section, subjecting the tissue section to steam heating in the presence of EDTA to assist in the unmasking of the antigen sites, preparing the tissue section from a sample that originated from a patient at risk for developing a cancerous condition, preparing the tissue section from a sample that originated from a patient currently receiving treatment for a present cancer condition (see whole document, especially pages 145-161). They

also teach in the identifying step, the somatic cell is recognized by immunohistochemical staining for p53 (page 153-160). They teach the somatic cell contains altered levels of PCNA and other p53 related proteins (page 153-160).

One of ordinary skill at the time the invention was made would have been motivated to apply Taylor et al's immunohistochemical staining for p53 to Diamandis et al's method for determining mutation load in order to enhance the sensitivity of immunohistochemical methods as applied to routinely processed paraffin sections (page 159). It would have been prima facie obvious to apply Taylor et al's immunohistochemical staining for p53 to Diamandis et al method for determining mutation load in order to enhance the sensitivity of immunohistochemical methods as applied to routinely processed paraffin sections in order to reduce the false negative results immunostaining results and increase the accuracy of the diagnosis (page 159).

6. Claims 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Diamandis et al (US 6, 071, 726 June 6, 2000) in view of Taylor et al., "Antigen Retrieval for Immunohistochemistry," Applied Immunohistochemistry, 4(3): 144-166, 1996 and in further view of Link, Jr. et al (US 6, 342, 217 B1 January 29, 2002).

The teachings and suggestions of Diamandis et al and Taylor et al. have been discussed previously.

Diamandis et al and Taylor et al do not teach radiation, cytotoxic or gene therapy treatment for cancer.

Link, Jr. et al teach radiation, cytotoxic or gene therapy treatment for cancer (see whole document, especially col. 3, lines 10-64).

One of ordinary skill at the time the invention was made would have been motivated to apply Link, Jr. et al's cancer treatments to Diamandis et al's and Taylor et al's combined method for determining mutation load using immunohistochemical staining methods in order to kill neoplastic cells (abstract). It would have been prima facie obvious to apply Link, Jr. et al's cancer treatments to Diamandis et al's and Taylor et al's combined method for determining mutation load using immunohistochemical staining methods in order to kill neoplastic cells.

7. Claim 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Diamandis et al (US 6, 071, 726 June 6, 2000) in view of Taylor et al., "Antigen Retrieval for Immunohistochemistry," Applied Immunohistochemistry, 4(3): 144-166, 1996 and in further view of Havemann et al (US 2002/0098166 A1 July 25, 2002).

The teachings and suggestions of Diamandis et al and Taylor et al. have been discussed previously.

Diamandis et al and Taylor et al do not teach mdm2 or vEGF.

Havemann et al teach the p53 regulated proteins of mdm2 (paragraph 150) and vEGF (paragraph 74).

One of ordinary skill at the time the invention was made would have been motivated to apply Havemann et al's p53 regulated proteins of mdm2 and vEGF to Diamandis et al's and Taylor et al's combined method for determining mutation load using immunohistochemical staining methods in order to isolate somatic cells (columns 1-3). It would have been prima facie obvious to apply Havemann et al's p53 regulated proteins of mdm2 and vEGF to Diamandis et

al's and Taylor et al's combined method for determining mutation load using immunohistochemical staining methods in order to isolate somatic cells.

8. Claims 17 & 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Diamandis et al (US 6, 071, 726 June 6, 2000) in view of Allalunis-Turner et al "Isolation of two cell lines from a human malignant glioma specimen differing in sensitivity to radiation and chemotherapeutic drugs" Radiat Res 1993 Jun; 134(3):349-54 and in further view of Rozemuller et al "Sensitive detection of p53 mutation: analysis by direct sequencing and multisequece analysis" Cancer Detec Prev 2001; 25(2):109-16 and Newton *PCR Essential Data*, John Wiley & Sons Ltd, 1995, pages 49-56.

The teachings and suggestions of Diamandis et al have been discussed previously.

Diamandis et al do not teach a 30 bp primer matching SEQ. ID. No. 1 and a 30 bp primer matching SEQ. ID. NO. 2.

Allalunis-Turner et al teach 3407 bp nucleotide sequence which shares a 30 bp region with SEQ. ID. NO. 1 of the instant application starting at locus 1483 (see Figure A of Result 2 on STIC Report).

Rozemuller et al teach direct sequencing of all exons of the p53 gene and RNA (abstract). They also teach 20303 bp nucleotide sequence which shares a 30 bp region with SEQ. ID. NO. 2 of the instant application starting at locus 14862 (see Figure B of Result 5 on STIC Report).

Newton teaches primer design that maximizes both the specificity and efficiency of the amplification reaction (page 49). They teach 13 primer-dependent parameters that would determine specificity and efficiency (page 49). They also teach primer labeling (page 53).

One of ordinary skill at the time the invention was made would have been motivated to apply Allalunis-Turner et al's 30 bp region, Rozemuller et al's 30 bp region, and Newton's primer design to Diamandis et al's method for determining mutation load in order to produce a specific and efficient primer for amplification. It would have been prima facie obvious to apply Allalunis-Turner et al's 30 bp region, Rozemuller et al's 30 bp region, and Newton's primer design to Diamandis et al's method for determining mutation load in order to produce a specific and efficient primer for amplification.

9. Claims 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Diamandis et al (US 6, 071, 726 June 6, 2000) in view of Allalunis-Turner et al "Isolation of two cell lines from a human malignant glioma specimen differing in sensitivity to radiation and chemotherapeutic drugs" Radiat Res 1993 Jun; 134(3):349-54 and in further view of Felix et al "Hereditary and acquired p53 gene mutations in childhood acute lymphoblastic leukemia" J Clin Invest 1992 Feb; 89(2):640-7 and Newton *PCR Essential Data*, John Wiley & Sons Ltd, 1995, pages 49-56.

The teachings and suggestions of Diamandis et al in US 6, 071, 726 and Allalunis-Turner et al have been discussed previously.

Diamandis et al do not teach a 33 bp primer matching SEQ. ID. NO. 3.

Felix et al teach 133 bp nucleotide sequence which shares a 33 bp region with SEQ. ID. NO. 3 starting at locus 53 (see Figure C of Result 1 on STIC Report).

Newton teaches primer design that maximizes both the specificity and efficiency of the amplification reaction (page 49). They teach 13 primer-dependent parameters that would determine specificity and efficiency (page 49). They also teach primer labeling (page 53).

One of ordinary skill at the time the invention was made would have been motivated to apply Allalunis-Turner et al's 30 bp region, Felix et al's 33 bp region, and Newton's primer design to Diamandis et al's method for determining mutation load in order to produce a specific and efficient primer for amplification. It would have been prima facie obvious to apply Allalunis-Turner et al's 30 bp region, Felix et al's 33 bp region, and Newton's primer design to Diamandis et al's method for determining mutation load in order to produce a specific and efficient primer for amplification.

10. Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Diamandis et al (US 6, 071, 726 June 6, 2000) in view of Murphy (WO 9906598 February 11, 1999) and Newton *PCR Essential Data*, John Wiley & Sons Ltd, 1995, pages 49-56.

The teachings and suggestions of Diamandis et al have been discussed previously.

Diamandis et al do not teach a 24 bp primer matching SEQ. ID. NO. 5.

Murphy teaches a 28 bp primer which shares a 24 bp region with SEQ. ID. NO. 5 of the instant application starting at locus 5 (see Figure D of Result 1 on STIC Report; example 6, page 46 in document). Murphy also teaches primers for amplifying DNA containing a p53 mutation.

Newton teaches primer design that maximizes both the specificity and efficiency of the amplification reaction (page 49). They teach 13 primer-dependent parameters that would determine specificity and efficiency (page 49). They also teach primer labeling (page 53).

One of ordinary skill at the time the invention was made would have been motivated to apply Murphy's 28 bp primer and Newton's primer design to Diamandis et al's method for

determining mutation load in order to produce a specific and efficient primer for amplification. It would have been prima facie obvious to Murphy's 28 bp primer and Newton's primer design to Diamandis et al's method for determining mutation load in order to produce a specific and efficient primer for amplification

## SUMMARY

11. No claims allowed.

## CONCLUSION

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shar Hashemi whose telephone number is (703) 305-4840 and whose e-mail address is shar.hashemi@uspto.gov. However, the Office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner is on flex-time schedule and can be best reached on weekdays from 7:00 a.m. to 3:30 p.m. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119.

Any inquiry of a general nature, matching or filed papers or relating to the status of this application or proceeding should be directed to the Sharon Thornton for Art Unit 1637 whose telephone number is (703)-305-3001.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official

Gazette, 1096 OG 30 (November 15, 1989). The CM1 Center numbers for Group 1600 are Voice (703) 308-1235 and Before Final FAX (703) 872-9306 or After Final FAX (703) 308-9307.

September 11, 2002

JEFFREY SIEW
PRIMARY EXAMINER
9/13/02